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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/916,849	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 1-122 is/are pending in the application.

4a) Of the above claim(s) 1,2,13,14,23,24,33,34,45,46,57, 58 and 69-122 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 3-12,15-22,25-32,35-44,47-56 and 59-68 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date Sep 16, 2002.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of applications election of Group I drawn to methods of classifying a tumor and methods of testing a subject, and the further election of SEQ ID NO:3. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP ' 818.03(a)).

Claims 1-122 are pending. It is noted that the restriction requirement had a typographical error which indicated that Group I encompasses claims 1-67. Upon review it has been ascertained that group I encompasses claims 1-68. Claims 1, 2, 13, 14, 23, 24, 33, 34, 45, 46, 57 and 58, drawn to non-elected inventions, are withdrawn from consideration. Claims 3-12, 15-22, 25-32, 35-44, 47-56 and 59-68 are examined on the merits. Claims 4, 5, 10, 12, 22, 32, 36, 37, 42, , 43, 48, 49, 54, 55, 60, 61, 65 and 66 will be examined to the extent that they read on SEQ ID NO:3.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 30, line 28; page 36, line 28; page 65, line 11, page 69, line 12, page 73, lines 12, 14 and 28; page 74, line 2; and page 100, line 25. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Applicant is advised to carefully check the specification for any other recitations of browser executable code.

The claims have been re-numbered consecutively according to Rule 1.26, however, a complete response to this action must include a properly numbered set of claims.

Claims 4, 5, 10, 12, 22, 32, 36, 37, 42, , 43, 48, 49, 54, 55, 60, 61, 66 and 67 are objected to for reciting non-elected inventions.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-11, 14-17, 21, 25-27, 31, 35-44 and 47-56, 59-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9, 21, 31 and 41, 53, 65 are vague and indefinite in the recitation of "detecting modification of a substrate". It is unclear how detection of the polypeptide of SEQ ID NO:3 can be further limited by "detecting modification of a substrate" by the polypeptide which is to be detected. further, the metes and bounds of "a substrate" and "a modification" are undefined.

Claims 10, 47 and 48 are vague and indefinite in the recitation of "stratifying a subject having the tumor for a clinical trial". It is unclear how said subject is to be "stratified". Further, it is unclear how said stratification contributes to the method objectives of classifying a tumor and testing a subject.

It is unclear how claims 14-17 further limit claims 3-5. Claims 2-5 have the method objective of classifying a tumor. Claims 14-17 recite a further l active step of providing further diagnostic, prognostic or predictive information based on the classifying step. It is unclear how the further active step contributes to the method objective of classifying a tumor.

It is unclear how claims 25-27 further limit claims 3-5. Claims 25-27 recite the active step of selecting a treatment based on the classifying step. It is unclear how this furthers the claim objective of classifying the tumor.

Claims 35 and 36 recite the method objective of "testing a subject". It is unclear how providing diagnostic, prognostic or predictive information based on the detecting step fulfills the method objective of 'testing a subject".

Claims 59 and 60 recite the method objective of "testing a subject". It is unclear how selecting a treatment based on the detecting step fulfills the method objective of testing a subject.

Claims 3, 4-10, 15-22, 25-31, 35-43, 47-55, 59-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. .

The instant claims are drawn to methods of classifying a tumor in a subject, methods of testing a subject, all methods comprising the detection of SEQ ID NO:3 or a gene encoding SEQ ID NO:3. the specification teaches that SEQ ID NO:3 is associated with a basal tumor subtype in breast tumors. the specification does not provide a description of tumors from any other organ which would express SEQ ID NO:3 as a diagnostic, prognostic marker. The genus of tumors encompassed by the claims is highly variant because it includes all tumor types. further, the genus of methods of testing a subject is even more variant, said method not confined to the testing of tumors. The art acknowledges that tumors are heterogeneous and much variation between tumor samples s possible. Thus, there is no nexus between the expression of SEQ ID NO:3 in a breast tumor and the expression of SEQ ID NO: in a non-breast tumor, it logically follows that the prognosis associated with the expression of SEQ ID NO:3 in a breast tumor would not anticipate the prognosis associated with SEQ ID NO:3 in a non-breast tumor. the upregulation of SEQ IDNO:3 in breast tumor tissue in no way anticipates the upregulation of SEQ ID NO:3 in non-tumor tissue. thus the disclosure of SEQ ID NO:3 associated with a basal tumor subtype in breast tissue and a poor prognosis in breast tumor patients having such a tumor does not adequately describe the genus of methods claimed. Further, the methods of testing a subject are not limited to methods of testing tumors but can apply to any pathological state. The specification does not provide any example other than a method of testing a breast tumor sample and evaluating the presence or absence of SEQ ID NO:3 found in association with said breast tumor sample. One of skill in the art would reasonably conclude that applicant was not in possession of the methods of classifying generic "tumors" , methods of and methods of testing a subject.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 3-6, 9, 12, 15-18, 21, 22, 35-38, 41-44, 67 and 68 are rejected under 35 U.S.C. 102(b) as being anticipated by Hackett et al (US 5,158,893).

Claims 3 and 4 are drawn to a method of classifying a tumor comprising the steps of providing a tumor sample; detecting expression or activity of a gene encoding the polypeptide of SEQ ID NO:3 in a sample; and classifying the tumor as belonging to a tumor subclass based on the results of the detecting step. claim 5 embodies the method of either claim 3 or claim 4 wherein the detecting step comprises detecting the polypeptide. Claim 6 embodies the method of claim 5 wherein the polypeptide is detected by performing immunohistochemical analysis on the sample using an antibody that specifically binds to the polypeptide. Claim 9 embodies the method of claim 5 wherein the detecting step comprises detecting modification of a substrate by the polypeptide. Claim 9 is included with the rejections because the metes and bounds of the claim are unclear for the reason set forth above. Claim 12 embodies the methods o claim 3 and 4 wherein the tumor is a breast tumor and the tumor subclass is a basal tumor. Claims 15-17 embody the methods of claim 3-5, respectively, further comprising providing diagnostic, prognostic or predictive information based on the classifying step. Claim 18 embodies the method of claim 17 wherein the polypeptide is detected by performing immunohistochemical analysis on the sample using an antibody that specifically binds to the polypeptide. Claim 21 embodies the method of claim 17 wherein the detecting step comprises detecting modification of a substrate by the polypeptide. claim 22 embodies the methods of claims 15 and 16 wherein the tumor is a breast tumor and the tumor subclass is a basal tumor.

Claims 35 and 36 are drawn to a method of testing a subject comprising the steps of providing a sample isolated from a subject; detecting the expression or activity of SEQ ID NO:3 in the sample; providing diagnostic, prognostic or predictive information based on the detecting

step. Claim 37 embodies the methods of claim 35 and 36 wherein the detecting step comprises detecting the polypeptide. Claim 38 embodies the method of claim 37 wherein the polypeptide is detected by performing immunohistochemical analysis on the sample using an antibody that specifically binds to the polypeptide. claim 41 embodies the methods of claim 37 wherein the detecting step comprises detecting modification of a substrate by the polypeptide. claim 42 embodies the methods of claims 35 and 36 wherein the sample is selected from a blood sample, a urine sample, a serum sample, an ascites sample, a saliva sample, a cell and a portion of tissue. Claim 43 embodies the methods of claim 35 and 36 wherein the sample is a tumor sample. Claim 44 specifies that the tumor sample of claim 43 is a breast tumor sample. claim 67 embodies the method of claims 35 or 36 wherein the sample is a tumor sample. claims 68 embodies the method of claim 67 wherein the tumor sample is a breast tumor sample.

Hackett et al disclose a method for detecting the 312C8-1 antigen in a breast tumor sample by means of immunohistochemistry, wherein the detection of said antigen is indicative of a human basal epithelium and wherein reactivity of a high proportion of malignant cells with the 312C8-1 monoclonal antibody also indicates an aggressive carcinoma with the associated prognosis of short survival time and early recurrence after surgical removal (column 11, line 65 to column 12, line 4). Hackett et al disclose that the 312C8-1 epitope is associated with a keratin which is restricted to the basal epithelium in a human mammary gland. Hackett et al do not specifically disclose that the 312C8-1 antigen is on the protein of SEQ ID NO:3 however, it appears to have the same distribution and prognostic significance as the detection of the instant SEQ ID NO:3. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product on which the instant method depends. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claims 35-39 and 41-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Soppet (WO 98/21242).

The specific embodiments of claims 35-38 and 41-43 are set forth above. Claim 39 embodies the method of claim 37 wherein the polypeptide is detected by using an ELISA assay and an antibody which specifically binds to the polypeptide.

Soppett discloses a method for detecting cancer comprising detecting the overexpression of the calcitonin receptor (page 29, lines 9-16). Soppett discloses that the assaying of the calcitonin receptor levels in a tissues can be studies by immunohistochemical methods (page 29, lines 23-27) and by ELISA assay (page 30, lines 1-3). Soppett specifically discloses epitope-bearing portions of the calcitonin receptor as including ammo acid residues 49-60, 113-123, 145-154, 189-209 and 259 to 560 of sequence identifier 2. The residues 2388-2921 of the instant SEQ ID NO:3 are identical to residues 33-566 of the sequence identifier 2. Thus, antibodies which bind to said specific epitopes of the calcitonin receptor will also bind to the instant SEQ ID NO:3.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3-6, 9-12, 15-18, 21, 22, 25-28, 31, 32, 35-38, 41-44, 47-50, 53-56, 59-62 and 65-68are rejected under 35 U.S.C. 103(a) as being unpatentable over Hackett et al (US 5,158,893) in

view of Schlom ("Monoclonal Antibodies: They're More and Less Than You Think", In: Molecular foundations of Oncology, 1991, pp. 105-107).

The specific embodiments of claims 3-6, 9, 12, 15-18, 21, 22, 35-38 and 41-44 are set forth above and the teachings of Hackett et al which anticipate said claims. Claim 10 embodies the method of claims 3 or 4 wherein classifying the tumor comprise stratifying a subject having the tumor for a clinical trial. Claim 11 embodies the method of claim 10 wherein the tumor is a breast tumor. Claims 25-27 embody the methods of claims 3-5 wherein the methods further comprise selecting a treatment based on the classifying step. Claim 28 embodies the method of claim 27 wherein the polypeptide is detected by performing imunohistochemical analysis using an antibody that specifically binds to the polypeptide. Claim 31 is drawn to the method of claim 27 wherein the detecting step comprises detecting modification of a substrate by the polypeptide. Claim 32 embodies the methods of claims 25 and 26 wherein the tumor is a breast tumor and the subclass is a basal tumor subclass.

Claims 47 and 48 embody a method of testing a subject comprising the steps of providing a sample isolated from a subject; detecting expression or activity of a gene encoding the polypeptide of SEQ ID NO:3 and stratifying the subject for clinical trail based on the detecting step. Claim 49 embodies the methods of claim 47 and 48 wherein the detecting step comprises detecting the polypeptide. Claim 50 embodies the method of claim 49 wherein the polypeptide is detected by using an antibody that specifically binds to said polypeptide. claim 53 embodies the method of claim 49 wherein the detecting step comprises detecting modification of a substrate by the polypeptide. claim 54 embodies the method of claims 47 and 48 wherein the sample is selected from the group consisting of a blood sample, a serum sample, an ascites sample, a saliva sample, a cell and a portion of tissue. claim 55 embodies the method of claims 47 and 48 wherein the sample is a tumor sample. Claim 56 specifies that the tumor sample of claim 55 is a breast tumor sample.

Claims 59 and 60 are drawn to a method of testing a subject comprising the steps of providing a sample isolated from a subject; detecting the expression or activity of a gene encoding the polypeptide of SEQ ID NO:3 and selecting a treatment based on the detecting step. Claim 61 embodies the method of claims 59 and 60 wherein the detecting step comprises detecting the polypeptide. Claim 62 embodies the method of claim 61 wherein the polypeptide is

detected by performing immunohistochemcial analysis using an antibody which specifically binds to the polypeptide. Claim 65 embodies the method of claim 61 wherein the detecting step comprises detecting modification of a substrate by the polypeptide. claim 66 embodies the methods of claims 59 and 60 wherein the sample is selected from the group consisting of a blood sample, a serum sample, an ascites sample, a saliva sample, a cell and a portion of tissue.

Hackett et al teach the method wherein a breast tumor cell is classified as a basal tumor subtype and associated with a poor prognosis consisting of decreased survival time and early recurrence after surgical removal. Hackett et al suggest that 312C8-1 antibody conjugate can be administered to treat subjects having these specific carcinomas (column 12, lines 32-36). Hackett et al do not specifically teach selecting a treatment or stratifying a subject having the tumor for clinical trial.

Schlom teaches the administration of drug, toxin and radionuclide conjugates of monoclonal antibodies for the treatment of tumors (page 107-109).

It would have been prima facie obvious at the time the invention was made to put subjects having such a tumor into a clinical trail comprising the 312C8-1 conjugated or fused to a toxin or to other chemotherapeutic agent in order to increase the survival time and relapse time in said patients. One of skill in the art would be motivated to do so by the suggestion of Hacket et al on administering the conjugate of the 312C8-1 antibody, and the teachings of Schlom on the high state of the art regarding making and administering antibody conjugates in order to kill tumor cell in a patient.

Claims 3-7, 9-12, 15-19, 21, 22, 25-29, 31, 32, 35-39, 41-44, 47-51, 53-56, 59-63 and 65-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hackett et al (US 5,158,893) and Schlom ("Monoclonal Antibodies: They're More and Less Than You Think", In: Molecular foundations of Oncology, 1991, pp. 105-107) as applied to claims 3-6, 9-12, 15-18, 21, 22, 25-28, 31, 32, 35-38, 41-44, 47-50, 53-56, 59-62 and 65-68 above, and further in view of Kerr and Thorpe (Immunochemistry LabFax, 1994, pp. 175-178)..

Claims 7, 19, 29, 39, 51 and 63 embody the methods of claims 5, 17, 27, 37, 49 and 61 wherein the polypeptide is detected by performing an ELISA assay using an antibody that specifically binds to the polypeptide.

Hackett et a teach a method comprising immunohistochemistry comprising and antibody that specifically binds to the 312C8-1 epitope. Hackett et al do not specifically teach an ELISA assay for detecting the polypeptide which is bound by the 312C8-1 antibody.

Kerr and Thorpe teach that an ELISA assay is a standard means of detecting proteins to which an antibody binds. One of skill in the art would be motivated to detect the polypeptide to which 321C8-1 specifically binds by means of an ELISA assay by the teachings of Kerr and Thorpe on the routine nature of this assay.

Claims 3-6, 8-12, 15-18,20-22, 25-28, 30-32, 35-38, 40-44, 47-50, 52-56, 59-62 and 64-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hackett et al (US 5,158,893) and Schlom ("Monoclonal Antibodies: They're More and Less Than You Think", In: Molecular foundations of Oncology, 1991, pp. 105-107) as applied to claims 3-6, 9-12, 15-18, 21, 22, 25-28, 31, 32, 35-38, 41-44, 47-50, 53-56, 59-62 and 65-68 above, and further in view of Hoeffler et al (WO 99/40434).

Claims 8, 20, 30, 40, 52 and 64 embody the methods of claims 5, 17, 27, 37, 49, and 61, wherein the polypeptide is detected using an antibody array that comprises an antibody that specifically binds to the polypeptide.

Hackett et a teach a method comprising immunohistochemistry comprising and antibody that specifically binds to the 312C8-1 epitope. Hackett et al do not teach an antibody array comprising the 312C8-1 monoclonal antibody.

Hoeffler et al teach detection of tumor antigens comprising an antibody array.

It would have been prima facie obvious to one of skill in the art at the time the invention was made to incorporate the 321C8-1 antibody into ant antibody array for the classification of tumors and the testing of patients. One of skill in the art would have been motivated to do so by the teachings of Hoeffler et al on the use of antibody arrays.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (571) 272-0828. The examiner can normally be reached on Monday through Friday from 9 am to 6:30 pm. A message may be

left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 272-0871. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at 703-308-4357.

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Primary Examiner, Group 1642
02/22/04

KAREN A. CANELLA PH.D
PRIMARY EXAMINER